



General

Guideline Title

Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.

Bibliographic Source(s)

Quality Standards Subcommittee of the American Academy of Neurology, Practice Committee of the Child Neurology Society, Delgado MR, Hirtz D, Aisen M, Ashwal S, Fehlings DL, McLaughlin J, Morrison LA, Shrader MW, Tilton A, Vargus-Adams J. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review). Report of the Quality Standards Subcommittee of the AAN and Practice Committee of the Child Neurology Society. *Neurology*. 2010 Jan 26;74(4):336-43. [40 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2013.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (I-IV) are provided at the end of the "Major Recommendations" field.

Recommendations

Treatment of Localized or Segmental Spasticity

1. For localized/segmental spasticity in the upper and lower extremities of children with cerebral palsy (CP) that warrants treatment, botulinum toxin A (BoNT-A) should be offered as an effective and generally safe treatment (Level A). There is insufficient evidence to support or refute the use of BoNT-A to improve motor function in this population (Level U).
2. There is insufficient evidence to support or refute the use of botulinum toxin B (BoNT-B), phenol, and alcohol injections as a treatment for spasticity in children with spastic CP (Level U).

Treatment of Generalized Spasticity

3. Diazepam should be considered as a short-term antispasticity treatment in children with CP (Level B). There is insufficient evidence to support or refute the use of diazepam to improve motor function in this population (Level U).
4. There is insufficient evidence to support or refute the use of dantrolene for the treatment of spasticity in children with CP (Level U).
5. There is insufficient evidence to support or refute the use of oral baclofen for the treatment of spasticity or to improve motor function in children with CP (Level U).
6. Tizanidine may be considered for the treatment of spasticity in children with CP (Level C). There is insufficient evidence to support or refute the use of tizanidine to improve motor function in this population (Level U).
7. There is insufficient evidence to support or refute the use of continuous intrathecal baclofen (ITB) for the treatment of spasticity in children with CP (Level U).

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies*)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if: 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Evidence for Therapeutic Intervention

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement. **

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Childhood spasticity due to cerebral palsy

Note: *Spasticity* (according to the Taskforce on Childhood Motor Disorders) is hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement; 2) resistance to externally imposed movements rises rapidly above a threshold speed of joint angle.

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Pediatrics

Pharmacology

Intended Users

Pharmacists

Physicians

Guideline Objective(s)

To evaluate published evidence of the efficacy and safety of pharmacologic treatments for childhood spasticity due to cerebral palsy

Target Population

Interventions and Practices Considered

Treatment

1. Oral medications (benzodiazepines [diazepam], dantrolene, baclofen, and tizanidine)
2. Neuromuscular blocking agents (botulinum toxins A and B [BoNT-A and BoNT-B])
3. Chemical denervation (phenol and alcohol)
4. Intrathecal baclofen (ITB)

Major Outcomes Considered

- Spasticity scores
- Dose-effect correlation
- Upper and lower extremity function
- Adverse side effects of pharmacological therapies

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2010 Guideline

Literature searches of MEDLINE and EMBASE were conducted for relevant articles published from 1966 to July 2008 using the following key text and index words: cerebral palsy, static encephalopathy, spasticity, hypertonia, children, and infantile. Key text and index words for the intervention included diazepam, Valium, tizanidine, Zanaflex, dantrolene, Dantrium, baclofen, Lioresal, intrathecal baclofen, phenol, alcohol, botulinum toxin A, Botox, Dysport, BTX-A, BoNT-A, botulinum toxin B, BoNT-B, BTX-B, Myobloc, and Neurobloc.

The inclusion criteria were all foreign languages with English abstracts, human subjects, peer reviewed, patients 19 years of age or younger with cerebral palsy (CP), and more than 9 patients studied. Citations of review articles from 2000 to 2008 were checked for additional pertinent references.

A total of 978 abstracts were initially found. From these, 528 were identified as potentially pertinent and reviewed in full. Finally, 218 articles were selected that fulfilled the inclusion/exclusion criteria.

2013 Reaffirmation

Medline and EMBASE were searched from 2010 February to 2013 July 13, using the following search terms: cerebral palsy, static encephalopathy, spasticity, hypertonia, children, and infantile. Key text and index words for the intervention included diazepam, Valium, tizanidine, Zanaflex, dantrolene, Dantrium, baclofen, Lioresal, intrathecal baclofen, phenol, alcohol, botulinum toxin A, Botox, Dysport, BTX-A, BoNT-A, botulinum toxin B, BoNT-B, BTX-B, Myobloc, and Neurobloc. The inclusion criteria were all foreign languages with English abstracts, human subjects, peer reviewed, patients 19 years of age or younger with cerebral palsy, and more than 9 patients studied.

Number of Source Documents

218 articles were selected that fulfilled the inclusion/exclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Therapeutic Intervention

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Each article was reviewed, abstracted, and classified by at least 2 authors. Disagreements were resolved by reaching consensus among the

reviewers, the first author, and at least two other authors.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2010 Guideline

The American Academy of Neurology (AAN) convened a multidisciplinary author panel consisting of 5 pediatric neurologists, 2 developmental pediatricians, 1 pediatric physiatrist, 1 pediatric orthopedist, and 1 adult neurologist.

The AAN's 4-tiered classification scheme for therapeutic evidence was used to classify articles (see "Rating Scheme for the Strength of Evidence"), and the strength of the recommendation was linked to the evidence (see "Rating Scheme for the Strength of the Recommendations").

2013 Reaffirmation

An author conducted a literature search using the same criteria as presented in the original guideline. Because the guideline recommendations would not change given the new literature available, the committee voted to reaffirm the guideline, stating that the conclusions and recommendations are still valid.

Rating Scheme for the Strength of the Recommendations

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies*)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if: 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of this guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, Neurology® peer reviewers, and representatives from related fields.

This guideline was approved by the Quality Standards Subcommittee on February 7, 2009; by the AAN Practice Committee on April 10, 2009;

by the Child Neurology Society (CNS) Practice Committee on December 7, 2009; by the AAN Board of Directors on October 19, 2009; and by the CNS Board of Directors on December 11, 2009.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate treatment of spasticity in children and adolescents with cerebral palsy
- Reasons to treat spasticity include reducing pain and muscle spasms, facilitating brace use, improving posture, minimizing contractures and deformity, facilitating mobility and dexterity, and improving patient ease of care as well as hygiene/self-care

Potential Harms

Adverse effects of pharmacological agents

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Quality Standards Subcommittee of the American Academy of Neurology, Practice Committee of the Child Neurology Society, Delgado MR, Hirtz D, Aisen M, Ashwal S, Fehlings DL, McLaughlin J, Morrison LA, Shrader MW, Tilton A, Vargus-Adams J. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review). Report of the Quality Standards Subcommittee of the AAN and Practice Committee of the Child Neurology Society. *Neurology*. 2010 Jan 26;74(4):336-43. [40 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 Feb (reaffirmed 2013 Jul 13)

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Child Neurology Society - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology (AAN)

Guideline Committee

Quality Standards Subcommittee of the American Academy of Neurology

Practice Committee of the Child Neurology Society

Composition of Group That Authored the Guideline

Authors: M. R. Delgado, D. Hirtz, M. Aisen, S. Ashwal, D. L. Fehlings, J. McLaughlin, L. A. Morrison, M. W. Shrader, A. Tilton and J. Vargus-Adams

Quality Standards Subcommittee Members (2007-2009): Jacqueline French, MD, FAAN (*Chair*); Charles E. Argoff, MD; Eric Ashman, MD; Stephen Ashwal, MD, FAAN (Ex-Officio); Christopher Bever, Jr., MD, MBA, FAAN; John D. England, MD, FAAN; Gary M. Franklin, MD, MPH, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Robert G. Holloway, MD, MPH, FAAN; Donald J. Iverson, MD, FAAN; Steven R. Messé, MD; Leslie A. Morrison, MD; Pushpa Narayanaswami, MD, MBBS; James C. Stevens, MD, FAAN (Ex-Officio); David J. Thurman, MD, MPH; (Ex-Officio); Dean M. Wingerchuk, MD, MSc, FRCP(C); Theresa A. Zesiewicz, MD, FAAN

Financial Disclosures/Conflicts of Interest

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com

The authors report the following conflicts of interest: Dr. Delgado serves on the editorial board of Developmental Medicine and Child Neurology; has received research support from Abbott, Sciele Pharma, Inc., UCB, Allergan, Inc., the Hurst Foundation, the United Cerebral Palsy Research & Educational Foundation, the Linda and Don Carter Foundation, and the Crowley Carter Foundation; and estimates that 50% of his clinical effort is spent on assessment and management of motor disorders of childhood, which includes treating children with cerebral palsy with oral antispasticity medications, ITB, and botulinum toxin injections. Dr. Hirtz reports no disclosures. Dr. Aisen serves as Medical Director of Cerebral Palsy International Research Foundation. Dr. Ashwal serves on the editorial board of Pediatric Neurology; receives royalties from publishing Pediatric Neurology: Principles and Practice (Elsevier, 2006); and receives research support from the NIH [R01 NS054001-01 (PI); 1R01NS059770-01A2 (PI)]. Dr. Fehlings has received speaker honoraria and funding for travel from RX Media; receives research support from Allergan, Inc., the Canadian Institutes of Health Research (CIHR), Social Sciences and Humanities Research Services (SSHRS), the Bloorview Research Institute, and Physician Services Inc.; and estimates 50% of her clinical effort is spent on spasticity intervention including botulinum toxin injections and ITB. Dr. McLaughlin has received research support from Medtronic, Inc., the NIH [NINDS NO1-HD-3-3351 (site PI), 1 U01 AR52171-01 (site PI), 1RC 1HD063838-01 (site PI)], and United Cerebral Palsy Research & Education Foundation; and spends 10% of his time evaluating and managing children with oral medications, baclofen pumps, and botulinum toxin. Dr. Morrison serves on the editorial boards of the Journal of Child Neurology and Pediatric Neurology and estimates that <1% of her clinical effort is spent on skin biopsy and <1% on lumbar puncture. Dr. Shrader has received funding for travel from Stryker and has received research support from Stryker, Smith and Nephew, Biomet, and VQ Orthocare. Dr. Tilton has served on a speakers' bureau for and received speaker honoraria and funding for travel from Medtronic, Inc.; has received research support from Allergan, Inc.; holds patent rights on a non-neurologic application of botulinum toxin (under consideration for licensure to her institution); and estimates 8%–10% of her clinical effort is spent on botulinum toxin injections and 10%–15% on intrathecal baclofen pumps. Dr. Vargus-Adams receives research support from the NIH [K23 HD049552 (PI), NICHD-2005-13-2 (Co-I), U01 AR057940-01 (Co-I)] and the Ohio Division of Emergency Medical Systems; her immediate family member holds financial interest in Novartis, Dermik Laboratories, Inc., and Proctor & Gamble and holds equity interest in Proctor & Gamble, Ligand, and GlucoWatch; and estimates 3% of her clinical effort is spent on intrathecal baclofen test dose and management, 15% on botulinum toxin injections, and 2% on phenol nerve blocks.

Guideline Status

This is the current release of the guideline.

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This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

A list of American Academy of Neurology (AAN) guidelines, along with a link to this guideline, is available at the [AAN Web site](#)

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 201 Chicago Avenue South, Minneapolis, MN 55415.

Availability of Companion Documents

The following is available:

- Pharmacological treatment of spasticity in children and adolescents with cerebral palsy. American Academy of Neurology (AAN) summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2010. 2 p. Available from the [AAN Web site](#) .
- Pharmacological treatment of spasticity in children and adolescents with cerebral palsy. Case study. St. Paul (MN): American Academy of Neurology. 2010. 5 p. Available from the [AAN Web site](#) .
- Pharmacological treatment of spasticity in children and adolescents with cerebral palsy. Slide presentation. St. Paul (MN): American Academy of Neurology. 2010. 52 pg. Available from the [AAN Web site](#) .
- Pharmacological treatment of spasticity in children and adolescents with cerebral palsy. Poster. St. Paul (MN): American Academy of Neurology. 2010. 1 p. Available from the [AAN Web site](#) .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the [AAN Web site](#) .

Patient Resources

The following are available:

- Cerebral palsy: drug treatments for spasticity in children and adolescents. American Academy of Neurology (AAN) summary of Evidence-based Guideline for patients and their families. St. Paul (MN): American Academy of Neurology. 2010. 2 p. Available from the [AAN Web site](#) .
- AAN public service announcement (PSA) for a guideline on pharmacologic treatment of spasticity in children and adolescents with cerebral palsy. St. Paul (MN): American Academy of Neurology. 2010. Available for download from the [AAN Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on August 18, 2010. The currency of the guideline was reaffirmed by the developer in July 2013 and the summary was updated by ECRI Institute on December 22, 2015.

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